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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,855	10/31/2003	Jens Holm	04305/100M237-US1	9333

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,855	HOLM ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19-32,52-57,59,73 and 76-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-25,28,52-57,59,73 and 76-92* is/are rejected.

7)☒ Claim(s) *26,27 and 29-32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/06/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received April 6, 2006. Claims 1-17, 19-32, 52-57, 59, 73, 76-92 are pending and currently under examination.

Priority: The priority date is November 1, 2002.

Withdrawal of Objections and Rejections

The rejection of claims 1-17, 19, 53-57, 59, 76-80, 90-92 under 35 U.S.C. 102(e) as being anticipated by King et al. (US 20030039660) is withdrawn.

Maintenance of Objections and Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 19-22, 52-57, 59, 73, 76-92 are rejected again under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims read on a recombinant protein variant wherein the protein variant is a variant of a scaffold protein, wherein the scaffold protein has a three-dimensional folding pattern that is structurally similar to the naturally-occurring allergen. Thus, the claims read on any variant of a protein that has a similar 3-D structure to the

natural allergen. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification, while being enabling for the protein variants rMal d 1 (2781) (SEQ ID NO: 2) and rMal d 1 (2762) (SEQ ID NO: 3), and the protein variants to the scaffold protein Dau c 1, does not reasonably provide enablement for recombinant protein variants of a scaffold protein that as a similar 3-D structure to the naturally-occurring allergen because the search to find a suitable scaffold protein may be indefinite and the experimentation required is immense.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, (1) the amount of experimentation is immense because of the large number of allergens and the large number of potential scaffold proteins for each one; (2) the amount of guidance provided by the specification is minimal since there is no discussion of how closely the structures must match. One of skill in the art would have no idea what structural characteristics are most critical in assessing the similarity between the scaffold protein and the naturally-occurring allergen. Continuing, (3) the specification contains a few working examples of allergen-scaffold pairs, however, one of skill in the art may still need to search indefinitely for a scaffold protein that has a similar structure to the allergen, in addition to the indeterminate number of proteins that may or may not be classified as an allergen; As for the next Wands factor, (4) the nature of the invention is placement of epitopes from allergens onto structurally similar scaffold proteins to minimize the cross-reactivity of the vaccine to be produced. With regard to Factor (5), the prior art shows the Bet v 1-Mal d 1 (2619) pair (Holm et al. 2001 J Chrom B 756: 307-313; IDS) and the idea of producing modified allergens by preparing hybrids consisting of a small portion of the "guest" allergen of interest and a large portion of a homologous but poorly cross-reacting "host protein...a scaffold," (King et al., paragraph 0036, US 20030039660); (6) the relative level of skill in this art is very high, that of a doctoral level immunologist with several years experience; (7) the predictability of the art is minimal since a priori one of skill in the art would be unable to predict which protein might be structurally similar enough to function as a scaffold. Finally, (8) the

claims are enormously broad in the sense that an indeterminate number of proteins may or may not be classified as an allergen.

Based on this analysis, the conclusion that it would require undue experimentation to practice the instant invention is inescapable.

Applicant's arguments filed April 6, 2006, have been fully considered but they are not persuasive.

Regarding point (1), Applicants assert naturally occurring allergens are well known in the art and the skilled artisan in this field would know which proteins are regarded as an allergen in the context of the current invention. Applicants assert a large number of scientific publications and textbooks are devoted to describing and categorizing allergens and point to several specific examples. Furthermore, Applicants point to the specification as providing a general description of allergies, characteristics of allergens in disease, as well as methods to test for allergencitiy (page 3, lines 4-15, page 4 pages 1-16). However, Applicants have neglected to address the additional burden of identifying the potential scaffold protein of the allergen since it is the variant of the scaffold protein that is being claimed. Therefore, in addition to the burden of searching for an allergen through the large amount of literature, there would be additional burden, not to mention undue experimentation in selecting for the large number of potential scaffold proteins for each allergen.

With regard to points (2)-(4), Applicants point out that the application provides explicit guidance enabling a skilled user to practice the claimed invention without undue

experimentation, specifically that the scaffold protein has a level of sequence identity with the naturally occurring allergen of between 30-50% (p. 23 lines 5-9) and that the deconvoluted CD-spectra of the protein variant deviates less than 30% compared to the CD-spectra of the naturally occurring allergen (p. 36 lines 13-16). In addition, Applicants assert the application describes a sufficient number of working examples and that a lengthy list of suitable allergen – scaffold pairs, including specific allergens from different sources and their corresponding suitable scaffolds are provided on pages 29-36. It is noted that Applicants have successfully generated a recombinant protein variant of a scaffold protein, specifically the protein variant rMal d 1 2781 (SEQ ID NO: 2), rMal d 1 2762 (SEQ ID NO: 3), and protein variants wherein the scaffold protein is Dau c 1 (p. 31-32). Applicants further point to the specification as disclosing allergen scaffolds are proteins that have a sequence identity with the naturally occurring allergen of below 30 and 50% (p. 23 lines 5-9), having little or no ability to bind to naturally occurring allergen specific antibodies (p. 22 lines 10-22, p. 40 lines 6-14, p. 47 lines 7-34).

The specification does not appear to provide clear guidance as to what is required for a scaffold protein to be selected as structurally similar to the allergen protein. The specification discloses that structure similarity between two proteins can be assessed by the comparison of secondary structure elements of homogeneously folded proteins by circular dichroism (CD) spectroscopy (p. 62 Example 4). It is noted that Applicants have also described this method as an experimental approach to determine if the 3-D structures of two proteins share significant homologies. It is known

in the art that amino acid sequence identity of 50% does not guarantee structural similarity (Yuan et al. 1998 Proteins 30: 136-143), and that even a single point mutation in a polypeptide sequence can lead to surprising alterations in protein structure and activity (Sergel et al. 2000 J Virol 74: 5101-5107). Given that the art recognizes difficulties in identifying structurally homologous proteins and the lack of guidance in the in the specification concerning how one of ordinary skill in the art is to overcome these difficulties, it does not appear that Applicants' working examples convey to the claimed genus of all scaffold proteins of a naturally occurring allergen. In addition to comprising two or more primary mutations, the recombinant protein variant can further comprise one or more secondary mutations introduced into the scaffold protein which are not present in the corresponding position in the naturally occurring allergen. On page 42 of the specification, Applicants disclose secondary mutations may be a substitution, a deletion or an addition and provide general preferences regarding how many secondary mutations should be present. It is noted that Applicants have successfully introduced secondary mutations to the protein variants rMal d 1 2781 (SEQ ID NO: 2), rMal d 1 2762 (SEQ ID NO: 3), and protein variants wherein the scaffold protein is Dau c 1 (p. 49-61 Examples 1-2). However, given the unpredictability of the art, insertion and/or deletion of amino acids into a scaffold such that the length of the primary amino acid sequence is altered is unpredictable and it is not clear if the protein variant will have the ability to induce an immune response and have an increased binding affinity to IgE antibodies when compared to the scaffold protein.

Further, structurally homologous proteins that can be used as scaffold proteins reasonably include endogenous self proteins which, except in autoimmunity, are not recognized by self antibodies, and as such it is unclear how immunogenicity would be maintained since it is not inherently present. Further, it is known that allergenicity cannot be determined *a priori* on a structural basis, and as such experimentation is required to ensure that the claimed protein variants of a scaffold protein actually has a reduced ability to induce histamine release (Blumenthal et al. Allergens and Allergen Immunotherapy: 37-50).

Therefore, based upon the breadth of Applicants' claims, the unpredictability of maintenance of structure in light of substitutions of amino acid sequences, the difficulty in identifying homologous sequences for use in the instant invention, and the unpredictability concerning diminution of IgE binding and therefore allergenicity, plus all of the other factors discussed above, it appears that one of ordinary skill in the art would need to perform an undue amount of research in order to make and use the full breadth of Applicants' claimed invention.

Claims 1-17, 19-22, 52-57, 59, 73, 76-92 are rejected again under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a recombinant protein variant wherein the protein variant is a variant of a scaffold protein, wherein the scaffold protein has a three-dimensional folding pattern that is structurally similar to the naturally-occurring allergen. *Vas-Cath Inc. V. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." As stated above, a protein variant of a scaffold protein that has a three-dimensional folding pattern that is structurally similar to the naturally-occurring allergen. However, the skilled artisan cannot necessarily envision all the proteins with a similar 3-D structure to the allergen or which one is suitable for use as a scaffold protein. Furthermore, the number of allergens from which a scaffold protein is to be selected from is indeterminate itself since a particular protein may or may not be classified as an allergen. While the specification does contain a few working examples of allergen-scaffold pairs, it fails to disclose all scaffold proteins to all allergens along with the primary mutations that need to be introduced to the scaffold protein in order to achieve the increased affinity and/or binding capacity to IgE antibodies when compared to the scaffold protein. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

In their remarks, Applicants point out that providing working examples for all possible embodiments of an invention is not required. Instead, possession may be shown in a variety of ways including an actual reduction to practice, or any description of relevant, identifying characteristics, so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention (66 Fed. Reg., 1099 at 1105, Jan. 5, 2001). Applicants further assert the specification discloses many suitable and exemplary allergens (p. 29-36) in addition to teachings related to predicting the desired secondary structural similarity between the scaffold and allergen.

Applicant's arguments have been fully considered but they are not persuasive. Applicants have broadly claimed a recombinant protein variant with the ability to induce a protective immune response to a naturally occurring allergen, wherein the protein variant is a variant of a scaffold protein, said scaffold protein has a three-dimensional folding pattern that is structurally similar to that of the naturally occurring allergen, comprising two or more primary mutations spaced by at least one non-mutated amino acid residue. The identity of the allergen and scaffold can be anything in the broadest claims and are limited to Mal d 1 and Dau c 1 in dependent claims. It is noted that Applicants have successfully generated a recombinant protein variant of a scaffold protein, specifically the protein variant rMal d 1 2781 (SEQ ID NO: 2), rMal d 1 2762 (SEQ ID NO: 3), and protein variants wherein the scaffold protein is Dau c 1 (p. 31-32). The claims recite that the scaffold protein and protein allergen are to be structurally similar. In Example 4 of the instant specification, Applicants disclose the secondary

structure can be assessed by circular dichroism analysis to determine structural similarities between a naturally occurring allergen and a scaffold protein (p. 62-63). However, this appears to be an experimental approach and as disclosed in the example, if the spectra seem to be reasonably superimposable one may assume that the proteins probably belong to the same structural class (p. 62-63). It is known in the art that an amino acid sequence identity of 50% does not guarantee structural similarity (Yuan et al. 1998 Proteins 30: 136-143), and that even a single point mutation in a polypeptide sequence can lead to surprising alterations in protein structure and activity (Sergel et al. 2000 J Virol 74: 5101-5107).

The guidelines for the examination of patent applications under 35 U.S.C. 112, first paragraph, written description requirement, make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the genus (Federal Register Vol. 66, No. 4 pages 1099-111, January 5, 2001). As discussed above, the relevant structural features that are to be used in identifying structurally similar proteins are not well defined. In view of this, one of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus of all allergen hybrid proteins. Thus, Applicants were not in possession of the

claimed genus of all allergen hybrid proteins. Applicant is directed to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, § 1 Written Description Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 7-9, 11-14, 19-25, 28, 52-57, 76-78, 90-91 are rejected again under 35 U.S.C. 102(a) as being anticipated by Holm et al. (2001 J Chromatography B 756: 307-313; IDS). Holm et al. teach the surface areas shared by the major allergens of birch and apple, Bet v 1 and Mal d 1, was investigated using the 3-D structure model of Bet v 1, primary sequence alignment, and immunochemical methods (p. 308). In the materials and methods section, Holm et al. teach the subcloning of two Mal d 1 genes, 2619 and 2620, their expression, and subsequent purification from DH5α cells (p. 308; claims 55-57, 90-91). Figure 1 illustrates the sequence alignment of the amino acid sequences of Bet v 1.2801, Mal d 1 (2619), and Mal d 1 (2620) compared to 15 other Mal d 1 sequences exhibiting from 57-66% sequence identity (p. 310). On page 30 of the instant specification, Applicants disclose Mal d 1 (2620) is a Bet v 1 scaffold protein and disclose the list of mutations that the at least two primary mutations can be selected from. It can be assessed from Figure 1 that the amino acid sequence of Mal d 1 (2619) contains the amino acid differences E12V, P16A, H40T, and E76K (p. 310; claims 1, 5,

9, 19-25, 28, 76-78, 90-91). Since the recombinant Mal d 1 (2619) meets the limitations of instant claim 1 as a recombinant protein variant of a scaffold protein comprising two or more primary mutations as disclosed in the instant specification, the physical properties, such as having an increased binding capacity to IgE antibodies as compared to the scaffold protein should be inherently present (claims 1-3, 5, 8, 11, 52-54). At residue 20, recombinant Mal d 1 (2619) contains the amino acid Y, which is a variation from amino acid N in recombinant Mal d 1 (2620) and amino acid K in recombinant Bet v 1 (p. 310; claim 4). In figure 2, Holm et al. teach the surface similarity of Bet v 1.2801, Mal d 1 (2620), and Mal d 1 (2619) (panel I D and E). In panel I.B, Holm et al. disclose the conformational epitope covers a water accessible area of 900 A (p. 311; claims 12-14). Holm et al. also performed immunochemical experiments using a monospecific rabbit antibody raised against natural Bet v 1, wherein rBet v 1 forms a well-defined precipitate while the precipitate of variant Mal d 1 (2620) is less blurred, as compared to the precipitate of variant Mal d 1 (2619) (p. 312, figure 3; claim 7).

In their response, Applicants assert Holm et al. is not applicable as a 102 reference because it is description and comparison of the deduced amino acid sequence alignments and predicted structural similarity between Bet v 1.2801 and various naturally occurring Mal d 1 isoallergens. Holm provides a characterization of the differences between Bet v 1.2801 and the naturally occurring Mal d 1 isoallergens as substitutions and shows which ones are considered conservative substitutions, as observed in the sequence alignments. Therefore, Holm et al. is not instructive with

regard to making a recombinant protein variant by introducing two or more primary mutations spaced by at least one non-mutated amino acid residue according the instant claims. Applicants further assert the Holm et al. reference is silent regarding the elements recited in instant claim 1. Applicant's arguments have been fully considered but they are not persuasive.

Instant claim 1 is drawn to a recombinant protein variant with the ability to induce an immune response to a naturally occurring allergen, wherein the protein variant has the 3 elements recited in the claim: 1) the protein variant is a variant of a scaffold protein; 2) the recombinant protein variant comprises two or more primary mutations spaced by at least one non-mutated amino acid residue; 3) the recombinant protein variant has an increased binding affinity to IgE antibodies. The claim is not drawn to a method of making a recombinant protein variant but rather to the recombinant protein variant product. As outlined in the 102(a) rejection above, Holm et al. teach a recombinant protein variant that meets the elements of claim 1. Holm et al. teach the subcloning of two Mal d 1 genes, 2619 and 2620, their expression, and subsequent purification from DH5α cells. Mal d 1 (2620) is a Bet v 1 scaffold protein, and Mal d 1 2619 is a variant of Mal d 1 (2620). Therefore, Holm et al. do teach a recombinant protein variant of a scaffold protein as recited in claim 1. Further, since the recombinant variant Mal d 1 (2619) meets the element of instant claim 1 as a recombinant protein variant of a scaffold protein comprising two or more primary mutations as disclosed in the instant specification, the physical properties, such as having an increased binding capacity to IgE antibodies as compared to the scaffold protein should be inherently

present. The rejection of the instant claims under 35 U.S.C. 102(a) as being anticipated by Holm et al. is maintained.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 79-89, 92 are rejected again under 35 U.S.C. 103(a) as being unpatentable over Holm et al. (2001 J Chromatography B 756: 307-313). The teachings of Holm et al. are outlined above. Additionally, Holm et al. disclose the sequence alignment of the amino acid sequences of Bet v 1.2801, Mal d 1 (2619), and Mal d 1 (2620) compared to 15 other Mal d 1 sequences exhibiting from 57-66% sequence identity (p. 310). Figure 1 illustrates the sequence alignment of the amino acid sequences of Bet v 1.2801, Mal d 1 (2619), and Mal d 1 (2620) compared to 15 other Mal d 1 sequences exhibiting from 57-66% sequence identity (p. 310). In Figure 1, Holm et al. indicate amino acid residues from the Mal d 1 sequences that are identical to Bet v 1.2801 are shown on a red background, while conservative substitutions (V-I-L-M, F-Y-W, S-T-C, E-D, N-Q, K-R-H) are shown on cyan background (p. 310). For example, the rMal d 1 (2619) amino acid sequence contains the variations E12V, P16A, H40T, E76K. Holm et al. also disclose surface similarity analysis between Bet v 1 and the various Mal d 1 isoallergens to illustrate the degree of conserved surface area. In panel I.B, Holm et al. disclose the conformational epitope covers a

water accessible area of 900 A (p. 311). Holm et al. do not teach a protein variant comprising 5 to 12 primary mutations or the various physical differences such as increased binding capacity, CD-spectra deviations, or the solvent accessibility of the primary amino acid residues.

It would have been obvious to a person having ordinary skill in the art to obtain a recombinant protein variant, such as Mal d 1 (2619), which is a variant of a scaffold protein, and introduce additional mutations, such as 5-12, to the sequence because Holm et al. teach the sequence alignment of various Mal d 1 isoallergens, indicating both identical and conservative substitutions, including an idea of the surface-exposed amino acids they have in common with the Bet v 1 allergen (claims 1, 6, 79-82, 92). It would also have been obvious to a person having ordinary skill in the art to realize that the properties, such as degree of binding capacity, CD-spectra deviations, and solvent accessibility of the primary amino acid residues will be dependent on the number of amino acid variations introduced into a Mal d 1 protein or can be selected for based on the surface similarity analysis as disclosed by Holm et al. therefore these limitations are inherent to the specific recombinant protein that is created and/or obtained from the many variants that are disclosed by Holm et al. (claims 1, 6, 79-82, 92).

In their response, Applicants again assert there is nothing in the Holm et al. reference that would suggest or direct one skilled in the art to make the presently claimed recombinant proteins. However, as explained above in the 102(a) remarks by Examiner, instant claim is not drawn to a method of making recombinant protein

variants of a scaffold protein, but to an actual recombinant protein variant product, which is anticipated by Holm et al. The rejection of the instant claims under 35 U.S.C. 103(a) as being unpatentable over Holm et al. is maintained.

Claims 26-27, 29-32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

June 20, 2006

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER